## REMARKS

Status of the Application

Claims 1-29 were pending in the application at the time the Office Action was mailed. All were rejected. Claims 24 and 27 were objected to.

By this amendment, claims 1, 2, 4, 6, 7, 9-11, 15, 17-19, 21, and 24 have been amended; claims 5, 12-14, 28 and 29 have been canceled; and no new claims have been added. Therefore, claims 1-4, 6-11, and 15-27 are presently pending and before the examiner for consideration.

Claim Objections

Claims 24 and 27 were objected to for being in improper multiple dependent form. Claims 24 and 27 have herewith been amended to remove the improper multiple dependency.

Rejections Under 35 U.S.C. 112

Claims 19-23, 25 and 26 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action states there is insufficient antecedent basis for the limitation "said addition" in claim 19. To address this rejection, claim 19 has herewith been amended to remove recitation of "...said addition...."

Rejections Under 35 U.S.C. 102

Claims 1, 2, 7, 15, 17, 19-23, 25, 26, 28 and 29 were rejected under 35 U.S.C. 102(b) as being anticipated by Leclerc et al (Biotechniques, 29:590-601, 2000). Claim 1, from which all other pending claims depend, has been amended to include "a gene cassette encoding at least one modified protein selected from the group consisting of: a modified LuxA and a modified LuxB...." Although the Leclerc et al. reference describes a modified *firefly* luciferase, it does not teach or suggest a nucleic acid encoding a modified *bacterial* luciferase subunit such as modified LuxA and a modified LuxB. Accordingly, all of the pending claims are patentable over the Leclerc et al. reference.

Rejection Under 35 U.S.C. 103(a)-Andersen et al. in view of Hakkila et al.

Claims 1-14, 19-24, and 27-29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al. (Applied and Environmental Microbiology, 64:2240-2246, 1998) in view of Hakkila et al. (Analytical Biochemistry, 301:235-242, 2002). Claim 1 has herewith been amended to include the limitations "a gene cassette encoding at least one modified protein selected from the group consisting of: a modified LuxA and a modified LuxB" and "and wherein the half-life of the modified protein when expressed in a cell is shorter than the half-life of the wild-type form of the protein when expressed in the cell." The Office Action argues that the sequence encoding LuxA or Lux B described in the Hakkila et al. reference can be substituted for the sequence encoding GFP in the plasmid described in the Andersen et al. reference. Even if such combination were possible, the Office Action fails to make out a prima facie case of obviousness

because (1) the teaching or suggestion to make the claimed combination is not found in the prior art and (2) the prior art does not teach that there was a reasonable expectation of success that the proposed combination would work.1

*The teaching or suggestion to make the claimed combination is not found in the prior art*

With regard to the teaching or suggestion to make the claimed combination, the Office Action asserts:

> One would have been motivated to make such a modification in order to receive the expected benefit of quicker and more sensitive detection of analytes in whole-cell sensor bacteria as taught by Hakkila et al. Further, one would have been motivated to modify the LuxA and/or LuxB sequences of Hakkila et al with the tail-specific protease tag coding sequences of Andersen et al to observe fast dynamic phenomena. The modified luciferase would be better adapted to quickly identify an analyte due to the benefits of the luciferase protein, as taught by Hakkila et al, and quicker to turn-off a signal in the absence of analyte due to the benefits of the tail-specific protease tag, as taught by Andersen et al. Moreover, one would be motivated to replace the GFP coding sequence with that of a luciferase coding sequence to decrease the complexity of the instrumentation required to detect the reporter gene expression.

Although the Office Action makes this assertion, it does not cite any prior art that supports these assertions as required by *In re Vaeck.*[2] Moreover, although the present application might provide a suggestion or motivation to combine the Andersen et al. and

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[1] See MPEP 2143. "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

[2] *Id.* See also, *In re Fritch* 972 F.2d 1260 (Fed. Cir. 1992) ("The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.").

Hakkila at al. references, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious."[3]

*The prior art does not teach that there was a reasonable expectation of success that the proposed combination would work.*

With regard to the reasonable expectation of success requirement, the Office Action concludes without providing any specific reasoning that:

> Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Given *In re Vaeck*'s requirement that the reasonable expectation of success must be found in the prior art and not in applicant's disclosure, Applicants have thoroughly reviewed the Andersen et al. and Hakkila at al. references and have not found that they in any way even suggest the proposed substitution of the sequence encoding LuxA or Lux B as described in the Hakkila et al. reference for the sequence encoding GFP in the plasmid described in the Andersen et al. reference. The cited references certainly do not teach that the result of the proposed substitution would have a reasonable expectation of success at functioning or displaying the characteristic of the limitation of amended claim 1 ("wherein the half-life of the modified protein when expressed in a cell is shorter than the half-life of the wild-type form of the protein when expressed in the cell").

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[3] *Id.* See also, *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention").

Moreover, the specification itself shows that the outcome of such a substitution was unpredictable. For example, the experiments described in the present application generated the unexpected result that in bacterial cells, the addition of a carboxy-terminal tag affected the functional half-life of the Lux AB holoenzyme when the tag was added to *luxA* or to both *luxA* and *luxB,* but modification of *luxB* alone did not have a significant effect (see p. 15, lines 16-18 and p. 16, lines 8 and 9 of the specification). Further, modification of *luxA* and *luxB* generated different results depending on the cell type. In bacterial cells, modification of *luxB* alone did not significantly affect the duration of bioluminescence; but in yeast cells, modification of *luxB* alone was sufficient to decrease the duration of bioluminescence.

The Office Action appears to argue that any nucleic acid reporter could be substituted for the nucleic acid encoding GFP in the plasmid described in the Andersen et al. reference with the predictable outcome of a functional reporter that displays a shorter half-life than a corresponding unmodified reporter. The art to which the invention pertains is, however, notoriously unpredictable. In this case, it is well known that the structure of GFP varies considerably from that of the LuxAB heterodimer. While GFP does not require dimerization or interaction with other cofactors or substrates (other than oxygen) to fluoresce, the bacterial luciferase system requires the heterodimerization of LuxA and Lux B as well as an interaction with cofactors/substrates (e.g., an oxidoreductase and a long-chain fatty aldehyde substrate). Adding an exogenous peptide sequence to LuxA or LuxB could have any number of consequences that could result in a failure of the component to function. For example, as pointed out in the specification at lines 24-27, page 15, it was speculated a modification to the carboxy-terminus of LuxA

would impact enzymatic activity, since the carboxy terminus of LuxA was thought to be involved in substrate binding at the time the application was filed.[4]

In view of the foregoing, each of the claims as amended are patentable over the combination of the Andersen et al. and Hakkila et al. references. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. 103(a)-Vieites et al. in view of Mateus and Avery, and Berset et al.

Claims 1, 2, 7, 15-21, 25, 26, 28 and 29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Vieites et al. (Yeast, 10:1321-1327, 1994) in view of Mateus and Avery (Yeast, 16:1313-1323, 2000) as evidenced by Berset et al. (Molecular and Cellular Biology, 22:4463-4476, 2002). The Office Action did not reject claims 5, 6, or 12-14 under this section. Each of these claims includes a limitation indicating that the modified protein is at least one of LuxA or LuxB. Claim 1, from which all other pending claims depend, has herewith been amended to include the limitation "a gene cassette encoding at least one modified protein selected from the group consisting of: a modified LuxA and a modified LuxB...." Accordingly, all pending claims are believed to be patentable over the combination of Vieites et al., Mateus and Avery, and Berset et al. references.

Conclusion

The currently pending claims before the examiner are supported throughout the specification and are patentable over the prior art. No new matter

[4] See, e.g., Valkova, N.R.S., and E.A. Meighen, Biochem., 38:13820-13828, 1999 (in Supplemental IDS filed concurrently with this Response).

has been added. This application is now in full condition for allowance, and such action is respectfully requested.

This amendment is accompanied by a request for a retroactive extension of time. The Commissioner is hereby authorized to charge the fee for the retroactive extension of time as well as any underpayment or credit any overpayment of fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 50-3110.

The examiner is cordially invited to call the undersigned if clarification is needed on any matter within this response, or if the examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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